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A Recyclable Fluorous (*S*)-Pyrrolidine Sulfonamide Promoted Direct, Highly Enantioselective Michael Addition of Ketones and Aldehydes to Nitroolefins in Water

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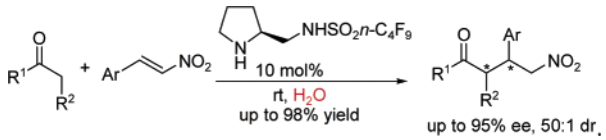
ABSTRACT



A recycle and reusable fluorous (*S*)-pyrrolidine sulfonamide organocatalyst has been developed for promoting highly enantio- and diastereoselective Michael addition reactions of ketones and aldehydes with nitroolefins in water. The organocatalyst is conveniently recovered from the reaction mixtures by fluorous solid-phase extraction and can be subsequently reused (up to six cycles) without a significant loss of catalytic activity and stereoselectivity.

Environmental concerns associated with chemical processes have encouraged the development of more environmentally friendly (greener) organic reactions. In recent years, reactions that take place in the environmentally clean, safe, and cheap solvent water have received considerable interest.[1] A great deal of effort has gone into the development of asymmetric organic reactions in aqueous media with a main focus on processes promoted by organometallic substances.[1] Recently, organocatalysis has emerged as a new field in asymmetric synthesis.[2,3] With the scope of this field rapidly expanding, it is important to recognize the potential limitations and disadvantages associated with the use of organocatalysts. Typically, organocatalyzed processes are carried out in organic solvents. The development of organocatalytic enantioselective reactions that take place in water remains a challenging task.[4,5] In addition, high organocatalyst loadings (10−20 mol %) are generally required in order to complete the transformations in reasonable time scales. Paralleling this is the high cost of the chiral materials used to prepare the organocatalysts, which is a major concern especially when the catalysts are used for large scale reactions. Owing to these limitations, the development of recyclable and reusable organocatalysts that promote reactions in water is a significant goal needing to be addressed to expand applications of organocatalysis as part of an environmentally benign approach to fine chemical synthesis. In this communication, we describe the study of a recyclable and subsequently reusable chiral fluorous pyrrolidine sulfonamide that cata-

(1) For reviews on organic synthesis in water, see: (a) Lindstrom, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Kobayashi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209. (c) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; Wiley: New York, 1997. (d) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic & Professional: New York, 1998.

(2) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis-From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2005.

(3) For selected reviews regarding organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Special Issue on Asymmetric Organocatalysis. *Acc. Chem. Res.* **2004**, *37*, 487.

(4) A few examples of organocatalyzed reactions in pure water have been reported with a focus on aldol reactions; see: (a) Mase, N.; Nakai, Y.; Ohara, N.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 734. (b) Hayashi, Y.; Sumiya, T.; Takahashi, J.; Gotoh, H.; Urushima, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 958. (c) Tang, Z.; Yang, Z.-H.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Org. Lett.* **2004**, *6*, 2285. (d) Dickerson, T. J.; Janda, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 3220.

(5) During the preparation of this manuscript, a similar study was reported by Takabe and co-workers: Mase, N.; Watanabe, K.; Yoda, H.; Takabe, K.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 4966.

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lyzes highly enantioselective Michael addition reactions of ketones and aldehydes with nitroolefins in water.

In the past few years, organocatalyzed asymmetric Michael addition reactions of aldehydes and ketones with nitroolefins have been intensively studied because these processes afford synthetically useful γ-nitro carbonyl compounds.[6] However, all reactions of this type reported to date take place in organic solvents.[5−7] Recently, we showed that (*S*)-pyrrolidine trifluoromethanesulfonamide **I** serves as an effective organocatalyst for asymmetric Michael addition reactions between aldehydes and nitroolefins in *i*-PrOH (Figure 1).[6m] We

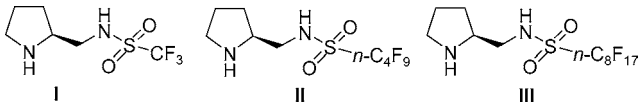
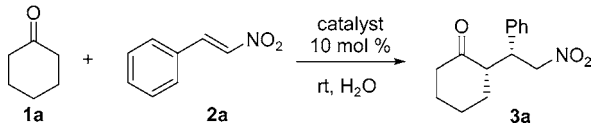


Figure 1. Chiral pyrrolidine sulfonamide organocatalysts.

envisioned that these reactions would also proceed in the protic solvent water. To test this hypothesis, the reaction of an aqueous solution of cyclohexanone **1a** and *trans*-β-nitrostyrene **2a** containing 10 mol % **I** (25 °C) was investigated. Indeed, the process took place smoothly, albeit slowly (30 h), to give Michael adduct **3a** in 90% yield with an 86% ee and 21:1 *syn*/*anti* ratio (Table 1, entry 1).

We surmised that more hydrophobic analogues of **I** would display greater activities as a result of enhanced aggregation between the organocatalysts and the substrates in the aqueous environment. Accordingly, more hydrophobic pyrrolidine sulfonamides **II** and **III** containing more lipophilic and strongly electron-withdrawing *n*-C_4F_9 and *n*-C_8F_{17} groups were designed and synthesized (Figure 1). Under the same

Table 1. Effect of Catalysts on Asymmetric Michael Addition Reaction of Cyclohexanone **1a** with *trans*-β-Nitrostyrene **2a**[a]



entry	catalyst	*t* (h)	% yield[b]	% ee[c]	dr[d]
1	**I**	30	90	86	21:1
2	**II**	9	95	90	27:1
3	**III**	40	93	88	24:1

[a] Reaction conditions: unless specified, cyclohexanone (**1a**) (196 mg, 2 mmol) and catalyst (7.62 mg, 0.02 mmol) in 0.4 mL of H_2O were stirred at room temperature for 20 min. Then *trans*-β-nitrostyrene (29.8 mg, 0.2 mmol) was added, and the resulting mixture was continued stirring at room temperature until completion of reaction, indicated by TLC. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H).

conditions, reaction of cyclohexanone with *trans*-β-nitrostyrene promoted by **II** occurred more rapidly (9 h) with improved yield (95%), ee (90%), and dr (27:1) (Table 1, entry 2). In contrast, a longer time (40 h) was needed to complete the process catalyzed by **III** (Table 1, entry 3), a result that is presumably due to the steric bulk of the *n*-C_8F_{17} group.

Recently, fluorous chemistry has emerged as a powerful strategy for facilitating catalyst recovery.[8−10] Introducing a fluorous tag into a catalyst can make it easily recoverable by using simple fluorous silica gel (silica gel with a fluorocarbon bonded phase) based solid−liquid extraction.[9c] By design, a *n*-C_4F_9 tag was incorporated into organocatalyst **II** so that it could be easily separated employing this technology. To test this feature, **II** (20 mol % employed to ensure the accuracy of evaluating catalyst recovery) was used to promote the Michael addition reaction of cyclohexanone with *trans*-β-nitrostyrene. Importantly, **II** was cleanly recovered (>90%) from the reaction mixture by using fluorous solid-phase extraction and the catalyst can be repeatedly reused (see Experimental Section). In each reuse, the recovered catalyst retains its high activity and high levels of enantioselectivity (89−90% ee) and diastereoselectivity (≥11:1 dr) even after six cycles (Table 2) despite some degree of loss of activity observed in cycles 2−6.

Having established that **II** can be easily separated and repeatedly reused, we next probed its use as a catalyst for a

(6) For selected examples of the organocatalytic asymmetric Michael addition of nitroolefins, see: (a) List, B.; Pojarliev, P.; Martin, H. J. *Org. Lett.* **2001**, *3*, 2423. (b) Enders, D.; Seki, A. *Synlett* **2002**, 26. (c) Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* **2003**, *5*, 2559. (d) Tian, S.; Ran, H.; Deng, L. *J. Am. Chem. Soc.* **2003**, *125*, 9900. (e) Tian, S.-K.; Chen, Y.-G.; Hang, J.-F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (f) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (g) Ishii, T.; Fiujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* **2004**, *126*, 9558. (h) Cobb, A. J. A.; Longbottom, D. A.; Shaw, D. M.; Ley, S. V. *Chem. Commun.* **2004**, 1808. (i) Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas, C. F. III. *Org. Lett.* **2004**, *6*, 2527. (j) Kotrusz, P.; Toma, S.; Schmalz, H.-G.; Adler, A. *Eur. J. Org. Chem.* **2004**, 1577. (k) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105. (l) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (m) Wang, W.; Wang, J.; Li, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 1369. (n) Tsogoeva, S. B.; Yalalov, D. A.; Hateley, M. J.; Weckbecker, C.; Huthmacher, K. *Eur. J. Org. Chem.* **2005**, 4995. (o) Hayashi, Y.; Gotoh, T.; Hayasji, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (p) Vakulya, B.; Varga, S.; Csampai, A.; Soos, T. *Org. Lett.* **2005**, *7*, 1967. (q) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (r) Wang, J.; Li, H.; Duan, W.-H.; Zu, L.-S.; Wang, W. *Org. Lett.* **2005**, *7*, 4713. (s) Luo, S.; Mi, X.; Zhang, L.; Liu, S.; Xu, H.; Cheng, J.-P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3093.

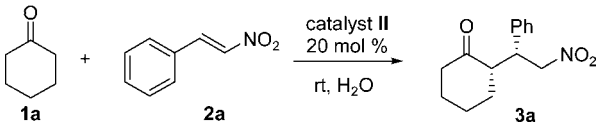
(7) Water as additive to facilitate reactions in organic solvents has been reported; for selected examples, see: (a) Sakthivel, K.; Nota, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260. (b) Brown, S. P.; Goodwin, N. C.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 1192 and references therein. (c) Nyberg, A. I.; Usanp. A.; Pihko, P. M. *Synlett* **2004**, 1891. (d) Xu, Y.; Cürdova, A. *Chem. Commun.* **2006**, 460. (e) Pihko, P. M.; Laurikainen, K. M.; Usano, A.; Nyberg, A. I.; Kaavi, J. A. *Tetrahedron* **2006**, *62*, 317.

(8) (a) Horváh, I. T.; J. Rábai, Sc*ience* **1994**, *266*, 72. (c) Curran, D. P.; Wipf, P.; Jeger, P.; Kim, S.-Y.; Ferritto, R.; Hadida, S.; Studer, A. Sc*ience* **1997**, *275*, 823. (c) Gladysz, J. A.; Curran, D. P.; Horváth, I. T. *Handbook of Fluorous Chemistry*; Wile-VCH: Weinheim, 2004.

(9) For selected reviews regarding fluorous chemistry, see: (a) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 1, 641. (b) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37. (c) Curran, D. P. *Synlett* **2001**, 1488. (d) Gladysz, J. A. *Chem. Rev.* **2002**, *102*, 3215.

(10) For selected examples of fluorous strategy for organometallic catalyst recovery and reuse, see: (a) Cavazzini, M.; Pozzi, G.; Quici, S.; Maillard, D.; Sinou, D. *Chem. Commun.* **2001**, 1220. (b) Croxtall, B.; Hope, E. G.; Stuart, A. M. *Chem. Commun.* **2003**, 2430. (c) Yao, Q. Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74. (d) Park, J. K.; Lee, H. G.; Bolm, C.; Kim, B. M. *Chem. Eur. J.* **2005**, *11*, 945. (e) Biffis, A.; Braga, M.; Cadamuro, S.; Tubaro, C.; Basato, M. *Org. Lett.* **2005**, *7*, 1841. (f) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636. (g) Dalicsek, Z.; Pollreisz, F.; Gomory, A.; Soós, T. *Org. Lett.* **2005**, *7*, 3243.

Table 2. Recycling and Reuse of Organocatalyst **II** in Promoting Michael Addition of Cyclohexanone **1a** to *trans*-β-Nitrostyrene **2a**[a]



1a **2a** **3a**

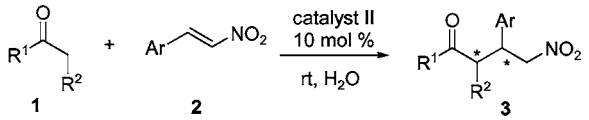
cycle	t (h)	% yield[b]	% ee[c]	dr[d]
1	6	92	90	34:1
2	9	95	90	33:1
3	10	90	90	33:1
4	14	95	89	36:1
5	24	85	89	22:1
6	50	70	89	11:1

[a] Unless specified, see footnote a in Table 1 and the procedure for catalyst recovery in Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H). [d] Determined by ^{1}H NMR.

wide range of Michael addition reactions between ketones and aldehdyes and nitroolefins (Table 3). The results showed that the reactions proceeded efficiently (60−98% yield) with high to excellent levels of enantioselectivity (68−95% ee) and diastereoselectivity (≥16:1 dr). The benchmark nitroolefins, which possess either neutral (entry 1), electron-donating (entries 2 and 3), or -withdrawing (entries 4 and 5) and heterocyclic groups (entry 6) and contain a variety of substitution patterns (*para* and *ortho*, entries 2−5), all participated in this catalytic process. Moreover, a variety of ketones underwent the catalytic process efficiently (83−85%) to give adducts with high ee (68−95%) and excellent dr (50:1) (entries 7 and 8). Aldehydes also could serve as effective Michael donors in highly enantioselective and diastereoselective reactions with *trans*-β-nitrostyrene (entries 9 and 10). Notably, two adjacent stereogenic centers are generated almost quantitatively and with good stereocontrol in the case of the linear chain aldehyde *n*-C_8H_{17} (entry 9). Even more significant is the observation that *i*-butyraldehyde undergoes **II**-catalyzed Michael addition with *trans*-β-nitrostyrene to furnish an adduct containing adjacent quaternary and tertiary carbon centers (entry 10).

In summary, the study described above has led to the development of fluorous (*S*)-pyrroldine sulfonamide **II**, the first easily separated and reusable fluorous organocatalysts that promotes highly enantio- and diastereoselective Michael addition reactions of ketones and aldehydes with nitroolefins in water. This effort has demonstrated that **II** is a robust catalyst that is effective in water and readily separated and reused without significant loss of catalytic activity and stereoselectivity. The full scope of applications of the new catalyst is currently being investigated. Given the rapidly ascending importance of both fluorous chemistry and organocatalysis, the strategy described here represents a general approach that should expand the scope of organocatalytic processes.

Table 3. Catalytic Asymmetric Michael Addition Reactions of Ketones and Aldehydes **1** with Nitroolefins **2**[a]



1 **2** **3**

entry	product	t (h)	% yield[b]	% ee[c]	dr[d]
1[c]	**3a**	9	95	90	27:1
2	**3b** (C_6H_4-*p*-OMe)	12	95	89	16:1
3	**3c** (C_6H_4-*o*-OMe)	12	92	91	50:1
4	**3d** (C_6H_4-*p*-Cl)	7	95	90	17:1
5	**3e** (C_6H_4-*o*-CF_3)	11	90	93	50:1
6	**3f**	9	91	85	17:1
7	**3g**	24	56 (83)[e]	95	50:1
8	**3h**	12	87	68	50:1
9	**3i** (*n*-C_7H_{15})	12	98	81	4:1
10	**3j**	18	60	86	-

[a] Unless specified, see footnote a in Table 1. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralpak AS-H or AD and Chiralcel OD-H). [d] Determined by ^{1}H NMR. [e] Yield based on recovered starting material.

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Supporting Information Available: Experimental procedures and spectra data for catalysts **II** and **III** and their intermediates and compounds **3a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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